

DIETARY FACTORS INFLUENCING THE DEVELOPMENT OF THE RUMINANT GASTROINTESTINAL TRACT

M. A. Steele, N. Malmuthuge and L. L. Guan
Department of Agricultural, Food and Nutritional Science
University of Alberta

The ruminant gastrointestinal tract (GIT) faces the challenge of protecting the host from the contents of the lumen, while controlling the absorption and metabolism of nutrients (Gaebel et al., 2001). In ruminant production, the GIT undergoes rapid development in early life leaving the young ruminant susceptible to gut health challenges. It is generally accepted that in all ruminant production sectors the neonatal and post-natal calves have significantly higher mortality and morbidity compared to the rest of the herd. Based on the most comprehensive survey available in the North America dairy industry (USDA, 2007), average mortality rates in dairy calves in the pre-weaning phase were estimated to be as high as 10% and morbidity rates over 46%, with gastrointestinal ailments being the number one culprit. Similarly, a survey conducted on commercial dairy farms in Ontario and Minnesota (2,874 calves from 0-3 months) reported that gastrointestinal infections were the first ailment experienced in the calf lifespan, with 23% of these calves requiring antibiotic treatment for diarrhea (Windeyer et al., 2014). In addition to a high degree of infections, antibiotic treatments and stress during the pre-weaning phase, calves have been traditionally limit-fed milk in dairy production at approximately 10% of bodyweight (half of normal consumption) and weaned early (Jasper and Weary, 2002; Khan et al., 2011). Weaning represents one of the most dramatic gastrointestinal transformations in nature and is associated with weaning distress, depressed growth and impaired gut health (Khan et al., 2011). Birth to weaning is a time of extreme gastrointestinal challenges in the young ruminants and the short-term and long-term biological outcomes of altered GIT development are poorly understood.

Over the past decade, several studies regarding young ruminants have challenged traditional feeding programs and showcased the benefits of enhancing early life nutrition to improve health, growth rates, feed efficiency, animal welfare and lifetime production (Jasper and Weary, 2002; Khan et al., 2011; Soberon et al., 2012; 2013). It is still unknown how many common nutritional practices in ruminant production impact GIT development, which represents an opportunity to improve health, performance and welfare. This review will focus on recent studies investigating how prenatal nutrition, colostrum management, pre-weaning feeding plane and weaning can impact gut development and health.

PRENATAL NUTRITION

Development of the GIT in ruminants begins during the first trimester (cattle – 30 days of gestation), followed by accelerated growth in the last trimester (Guilloteau et al., 2009). For example, the growth of the small intestine in bovine fetus during 175 – 280

days is two-fold higher than that of the whole body (Guilloteau et al., 2009). During this period of fetal development, maternal nutrition plays a vital role in the healthy growth of the GIT (Duarte et al., 2013). Restriction of maternal nutrition during early to mid-gestation is associated with variations in fetal gut development (Meyer et al., 2010); however, this is not the case during mid to late gestational nutrition restrictions (Duarte et al., 2013). These changes are mainly studied in terms of intestinal tract weight, crypt and villus development, as well as vascularity (Trahair et al., 1997; Meyer et al., 2010; Duarte et al., 2013). Nonetheless, the effect of maternal nutrition restriction on fetal gut development of calves and lambs has been suggested to vary depending on the dam's parity (Meyer et al., 2010). Nutritional restriction during the first half of the pregnancy decreases small intestinal weights of lambs born to multiparous ewes (Trahair et al., 1997). Although there are no differences observed in the small intestinal villus height and mucosa thickness, crypt depth has been decreased due to restricted maternal nutrition (Trahair et al., 1997). Moreover, the differentiation of enterocytes is abnormal in fetuses of nutrition-restricted ewes, compared to well-fed ewes (Trahair et al., 1997). In contrast, Meyer and colleagues (2010) reported an increase in intestinal vascularity and jejunal proliferation in calves born under restricted maternal nutrition during early gestation. The lack of studies and variation in results related to how prenatal nutrition can impact fetal GIT development of ruminants represents a great need and valuable opportunity to uncover more consistent results through future research.

COLOSTRUM FEEDING

Ruminant GIT development mainly occurs prenatally; however, it undergoes marked structural changes postnatally to adapt the dietary changes and to digest and absorb the nutrients (Guilloteau et al., 2009). Colostrum, the first diet of neonatal ruminants that facilitates passive transfer of immunity, has been shown to influence the early development of the GIT (Baumrucker et al. 1994; Blattler et al., 2001; Yang et al., 2015). Although the passive transfer of maternal antibody is the main focus of colostrum management in neonatal calves, growth factors (insulin-like growth factor- IGF-1 and hormones) present in colostrum have been shown to influence gut development (Baumrucker et al. 1994; Blattler et al., 2001). Feeding colostrum within the first 3 days of life enhances the growth of small intestinal villus (circumference, height) and crypt (depth) of neonatal calves, compared to that of formula milk (Blattler et al., 2001). However, these effects are more prominent in the duodenum compared to that of jejunum and ileum (Blattler et al., 2001), suggesting that the effect of colostrum may be more influential in the growth of proximal intestine than that of the distal intestine. Similarly, the rate of epithelial cell proliferation has increased with colostrum feeding compared to formula milk feeding (Blattler et al., 2001).

The feeding of IGF-1 in milk has been shown to increase epithelial proliferation in neonatal calves (Baumrucker et al., 1994). IGF is involved in a variety of metabolic and physiological activities, such as transmembrane transportation and metabolism of glucose, amino acids, and nucleotides, synthesis of proteins, regulation of cell proliferation and differentiation, as well as inhibition of apoptosis (Georgiev, 2008). The concentration of IGF-1 is highest in the first colostrum and gradually decreases over

time (Baumrucker et al., 1994). This suggests that the presence of high amounts of IGF-1 in colostrum, when compared to formula milk that contains only traces of IGF-1 (Blattler et al., 2001), may enhance the intestinal development of calves fed with colostrum. However, feeding of growth factors alone has less impact on intestinal morphology than feeding actual colostrum (Roffler et al., 2003), indicating that there are other colostral components that may influence the development of the neonatal intestine.

Feeding colostrum has also been shown to impact intestinal epithelial barrier functions in piglets, via inhibiting the epithelial cell apoptosis and stimulating mucin secretion (Oste et al., 2010; Puiman et al., 2011). Additionally, feeding colostrum increases the number of goblet cells and intestinal protein synthesis, compared to formula milk (Puiman et al., 2011), which also enhances the intestinal barrier functions. These enhanced intestinal barrier functions later decrease the incidence of necrotizing enterocolitis in pigs (Jensen et al., 2013), indicating that colostrum-driven changes in the intestinal barrier play a crucial role in host susceptibility to enteric infections. Feeding bovine colostrum has also been shown to lower necrotizing enterocolitis induced by formula milk feeding in preterm pigs by improving intestinal functions, such as lowering pro-inflammatory cytokines production and increasing villus height and brush-border enzyme activities (Stoy et al., 2014). While it is evident that feeding of colostrum soon afterbirth decreases the calf's susceptibility to enteric infections (Godden et al., 2012), there remains a lack of knowledge regarding the impact of colostrum feeding on intestinal barrier development in calves, as the majority of studies focus primarily on absorption of maternal immunoglobulin. Thus, it is necessary to further explore this area in order to fully understand the effects of colostrum feeding on the development of intestinal barrier functions and calf susceptibility to enteric infections.

Over the last decade, our knowledge of how gastrointestinal microbiota can impact metabolic diseases has been transformed by a series of experiments in rodent models (Turnbaugh et al., 2004). Adding to these findings is the evidence that colonization in the first day of life can have longstanding consequences on the gut microbiota and health later in life (Koeinig et al., 2011). Given these results, colostrum management during the first day of life could have a longstanding influence on the microbial community structure, and thus, a substantial impact on GIT development and health. Colostrum contains specific bacteria and a large collection of oligosaccharides that can impact microbiota in the newborn after feeding, which is why colostrum is often referred to as the complete probiotic/prebiotic (Mills et al., 2012). With respect to potential probiotic and/or prebiotic properties within colostrum in ruminants, a study comparing pasteurized versus fresh colostrum feeding determined that pasteurized colostrum maintained higher levels of *Bifidobacterium* colonization and less *E. coli* in the calf ileum during the first 12 hours of life (Malmuthuge et al., 2015). The pasteurized colostrum did not contain viable *Bifidobacterium*, leading the authors to speculate that the oligosaccharides in colostrum underwent structural changes, which specifically supported *Bifidobacterium* growth as a result of heat treatment. This study is the first to

show how on-farm feeding practices of colostrum to ruminants in the first day of life may play a key role in microbial colonization and gut development.

FEEDING PLANE

Calves have been traditionally limit-fed milk or milk-replacer in dairy production at approximately 10% of bodyweight (half of normal consumption) (Jasper and Weary, 2002). Over the past decade, it has been well established that increasing intake during the pre-weaning phase increases the growth rate of calves and potentially future production (Soberon et al., 2012; 2013). Yet very little is known about how this feeding strategy will impact gut development. Although elevated planes are being fed during the pre-weaning period, many of these feeding schemes still restrict milk intake during the initial week(s) of life. This may be due to the train of thought purporting that higher levels of milk in the first weeks of life increase the incidence of diarrhea, a notion that is completely unfounded scientifically (Soberon et al., 2012). A recent study by de Passille et al. (2014) suggests that calves that consume more milk in the first five days of life have greater intake, growth and health during the entire pre-weaning phase. Besides the quantity of milk in the first week of life, there may be opportunities to improve the quality of milk as well. For example, colostrum feeding has been mainly focused on maximizing the passive transfer of immunoglobulins before gut closure. However, other bioactive components, such as growth hormones, prebiotics and immune system stimulants elevated within colostrum and transition milk (milk collected from the first three days after parturition) may aid in the development and health of the GIT, but are often overlooked. Although, abrupt transition from whole milk to milk replacer after the first meal of life is often practiced, calves with free-access to colostrum during the first week displayed greater growth rates and transiently enhanced insulin status and reduced cortisol status (Hammon et al., 2002). In a recent study, it was determined that calves fed transition milk have elevated health status, however the specific impact on the gut has not been properly studied - an important aspect of this feeding practice (Conneely et al., 2013). More work related to the impact of elevated quantity and quality of nutrition during the first week of life and its impact on gut development would be of great value to our industry.

After the first meals of life, dairy calves are transitioned to a milk feeding scheme that is typically offered in less than two meals per day (Johnsen et al., 2015). This transition marks a stark contrast to the calves' natural tendency to nurse from their dams *ad libitum*, facilitating feedings of up to 10 times a day in the first weeks of life (Jensen, 2003). Increasing feeding frequency, when calves are fed larger volumes of milk, improves digestion and efficiency of nutrient utilization (van den Borne et al., 2006). This may also provide benefits to digestive health when compared to feeding two times a day. Ahmed et al. (2002) determined that increasing the number of meals raises abomasal luminal pH and reduces ulceration. If large quantities of milk are fed in two meals per day, the abomasal capacity may be surpassed and milk may overflow to the reticulorumen. This is often referred to as "ruminal drinking," and if prolonged, can result in bacterial fermentation of the milk, which may lead to ruminal acidosis, impaired abomasal curd formation and infection. There is evidence that feeding elevated planes

of nutrition in only two meals per day disrupts metabolic and endocrine functions, leading to insulin resistance and disturbed glucose metabolism in veal and dairy calves (Bach et al., 2013). The long-term implications of these findings on gut development and metabolism are unknown and require more detailed investigations.

WEANING

The most dramatic changes in diet and gut microbiota in the ruminant lifespan occur during weaning. In nature, the weaning process occurs gradually over many weeks when calves are left to nurse from their dams, and is completed at approximately 10 months of age (Jensen, 2003). In contrast, commercial production systems, such as dairy, where feeding milk is considered more costly than feeding solid feed, practice abrupt transitioning of calves from milk to solid feed as early as possible. Early weaning methods (1-2 months of life) were accomplished by encouraging solid feed intake early, through the restriction of milk feeding to approximately 10% of birth weight, less than half of *ad libitum* consumption (Khan et al., 2011). Weaning is marked by the rumen capacity increasing from 30 to 70% of the entire forestomach (Baldwin et al., 2004). This process requires an extensive increase in the surface area for the absorption of short chain fatty acids (SCFA) produced through ruminal microbial fermentation to meet the demands for growth. This results in tremendous gut and metabolic ramifications to calf growth rate, as tissues must convert from reliance on glucose supplied from milk to the metabolism of SCFA as primary energy substrates for gluconeogenesis in the liver (Baldwin et al., 2004). With the recent adoption of feeding elevated levels of milk, weaning becomes even more critical as solid feed intake prior to weaning will be depressed.

To date, most of the studies have focused on rumen development during weaning transition. Factors that contribute to ruminal development include: the onset of weaning, the level of dry matter intake, dietary starch, and probiotics in dry feed (Khan et al., 2011; Eckert et al., 2015). Of all of the proposed mechanisms of ruminal growth and development, ruminal butyrate has been reported to be the most potent stimulator of epithelial proliferation and differentiation (Sakata and Tamate, 1978; Baldwin et al., 2004). In addition, hormones such as IGF-1 and epidermal growth factor have also been shown to stimulate the proliferation and differentiation of rumen epithelial cells in culture (Baldwin et al., 2004). The rapid state of cellular proliferation and differentiation during weaning is often associated with the condition of ruminal parakeratosis (Bull et al., 1965). This is defined as an accumulation of the outermost layer of the epithelium, termed the corneum, which can reduce SCFA absorption.

Recently, a series of microarray experiments were conducted using rumen tissue comparing different diets (hay, grain and milk) to uncover the mechanisms governing rumen epithelial proliferation and differentiation. It was determined that transforming growth factor β 1 (Connor et al., 2014), peroxisome proliferator active receptors (Connor et al., 2013; Naeem et al., 2014) and microRNA (Liang et al., 2014) may be key target growth factors controlling cellular differentiation and inflammation. Understanding the control mechanisms for rumen growth and differentiation will offer insight into how to

perform dietary manipulations to smooth the transition from a pre-ruminant to a ruminant during weaning.

From a microbiological standpoint, rumen colonization starts immediately after birth. Within minutes, the rumen is colonized with microbes, and within two days of birth anaerobic bacteria colonize (Fonty et al., 1987). The appearance of adult-like cellulolytic and methanogenic bacteria as well as anaerobic fungi occurs in the first week of life (Fonty et al., 1987). A recent study using next generation DNA sequencing techniques confirms that the ruminal microbiota prior to weaning has a similar functional capacity as that of a mature ruminant (Li et al., 2012). The appearance of these populations is not dependent on nutrient digestion, as during this period the rumen has no functional activity, and may play a role in long-term imprinting of the microbial community (Jami et al., 2013). Although there has been great progress in the techniques used to study microbiology over the past decade, the microbial changes that occur during weaning remain poorly described.

While the rumen has received the bulk of the attention in the literature, it has recently been shown that the lower gut also undergoes transformation during weaning. It is hypothesized that the gastrointestinal tract barrier function is compromised during weaning. Associated with the disrupted barrier functions, feeding starter in combination with milk close to weaning tended to increase the mRNA expression of toll-like receptors that recognize bacteria (Malmuthuge et al., 2013). A recent study supports this notion of altered barrier function during weaning, showing increased permeability of the GIT during weaning (Wood et al. (2015), suggesting the importance of investigating the lower gut rather than the rumen in isolation. Infant and piglet research has clearly documented inflammation and morphological changes of the intestine during weaning (Pie et al., 2014). The same can be expected to occur in ruminants, as the levels of starch in the diet are equally high. An increase in inflammatory markers has been shown during the weaning of dairy calves (Kim et al., 2011). It may be that ruminants suffer temporarily from hindgut acidosis, for they have shown elevated fecal starch levels during weaning (Eckert et al., 2015). Greater investigation of the lower gut microbiological, structural, and functional changes and how these changes contribute to weaning stress is a logical next step in research.

CONCLUSION

It has become clear over the last decade that the nutrition of young ruminants in early-life can have longstanding impacts on growth, development and long-term productivity. The gut development, especially at weaning, is one of the most dramatic transformations in nature. In addition, the young ruminant is highly susceptible to gastrointestinal ailments prior to weaning that may have longstanding impacts on development. An understanding of how commonly practiced nutritional protocols can impact on gut development has not been achieved. In particular, few studies have looked directly at how gut development of the young ruminant is influenced by prenatal nutrition, colostrum feeding frequency and duration, pre-weaning level of feeding and weaning duration and age on gut health and development. Although it is necessary from

an agricultural production standpoint to measure growth during early-life nutrition program evaluation, there is also great value in measuring the dietary impact on gut development in order to achieve progress in this field.

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